18 September 2025
EMA/CHMP/258625/2025
Committee for Medicinal Products for Human Use (CHMP)

Consultation procedure Public Assessment Report (CPAR)

Consultation on an ancillary medicinal substance incorporated in a medical device

Medical device: Gynemed GmbH & Co. KG HSA-containing ART media

Ancillary medicinal substance: Human serum albumin

Procedure No.: EMEA/H/D/006611/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

ART	Assisted Reproductive Technology
CHMP	Committee for Medicinal Products for Human Use
CoA	Certificate of Analysis
CPAR	Consultation Public Assessment Report
CZE	Capillary Zone Electrophoresis
DP	Drug Product (Human Albumin 25%)
DS	Drug Substance (Human Albumin (bulk))
EMA	European Medicines Agency
EMCV	Encephalomyocarditis virus
ESHRE	European Society of Human Reproduction and Embryology
ET	Embryo transfer
EU	European Union
FCoS	Foetal cord serum
FDA	United States Food and Drug Administration
GMP	Good Manufacturing Practices
GT	Grifols Therapeutics LLC – North Carolina, USA
Gynemed	Gynemed GmbH & Co. KG HSA-containing ART media
HAS	Human albumin solution
HSA	Human serum albumin
HAV	Hepatitis A Virus
HCV	Hepatitis C virus
HIV-1	Human Immunodeficiency Virus type 1
HIV-2	Human Immunodeficiency Virus type 2
HPLC	High Performance Liquid Chromatography
HTF	Human tubal fluid
HSSA	Human Sperm Survival Assay
ICSI	Intra Cytoplasmic Sperm Injection
IG	Instituto Grifols S.A., Barcelona, Spain
ISO	International Organization for Standardization
IUI	Intra-uterine injection

IVF	*In vitro* fertilization
MA	Marketing Authorisation
MAH	Marketing Authorisation holder
MEA	Mouse Embryo Assay
MDCG	Medical Device Coordination Group
MDR	Medical Device Regulation
NBº	Notified Body
NAT	Nucleic acid testing
NLT	No Less Than
NMT	No More Than
OAB Stockholm	*Octapharma AB* – Stockholm, Sweden
OCABR	Official Control Authority Batch Release
OMCL	Official Medicines Control Laboratory
OPG Vienna	*Octapharma Pharmazeutika ProduktionsgesmbHIG* – Vienna, Austria
Ph. Eur.	European Pharmacopoiea
PE	Polyethylene
PMF	Plasma Master File
PPV	Porcine ParvoVirus
PRV	PseudoRabies Virus
Reo3	Reovirus type 3
RH	relative Humidity
SST	sperm Survival Test
USP	United States Pharmacopoeia
WNV	West Nile Virus

1. Background information on the procedure

1.1. Submission of the dossier

The notified body BSI Group, The Netherlands B.V. submitted to the European Medicines Agency (EMA) on 8 July 2024 an application for consultation on Human serum albumin incorporated as ancillary medicinal substance(s) in the medical device Gynemed GmbH & Co. KG HSA-containing ART media, in accordance with the procedure falling within the scope of Directive 93/42/EEC, as amended.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Antonio Gomez-Outes

Co-Rapporteur: Jayne Crowe

The application was received by the EMA on	8 July 2024
The procedure started on	3 October 2024
The Rapporteur's first Assessment Report was circulated to all CHMP members on	19 December 2024
The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	06 January 2025
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	30 January 2025
The applicant submitted the responses to the CHMP consolidated List of Questions on	03 March 2025
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	26 May 2025
The CHMP agreed on a list of outstanding issues to be sent to the applicant on	19 June 2025
The applicant submitted the responses to the CHMP List of Outstanding Issues on	29 August 2025
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	05 September 2025
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for quality and safety including the clinical benefit/risk profile of Human serum albumin as ancillary medicinal substance(s) used in Gynemed GmbH & Co. KG HSA-containing ART media on	18 September 2025

1.3. Manufacturers

1.3.1. Manufacturer(s) of the active substance used as ancillary medicinal substance

Grifols Therapeutics LLC (GT)
8368 US 70 Business Hwy. West, Clayton
North Carolina 27520, USA

Octapharma Pharmazeutika ProduktionsgesmbHIG (OPG Vienna)
Oberlaaer Strasse 235
1100 Vienna, Austria

Octapharma AB (OAB Stockholm)
Lars Forssells gata 23
11275 Stockholm, Sweden

1.3.2. Manufacturer(s) of the finished product used as ancillary medicinal substance

Grifols Therapeutics LLC (GT)
8368 US 70 Business Hwy. West, Clayton
North Carolina 27520, USA

Octapharma Pharmazeutika ProduktionsgesmbHIG (OPG Vienna)
Oberlaaer Strasse 235
1100 Vienna, Austria

Octapharma AB (OAB Stockholm)
Lars Forssells gata 23
11275 Stockholm, Sweden

1.3.3. Manufacturer responsible for import and batch release in the European Economic Area

Instituto Grifols S.A.
Calle De Can Guasch 2
Poligono Industrial Llevant
08150 Parets Del Valles
SPAIN

Octapharma Pharmazeutika ProduktionsgesmbHIG (OPG Vienna)

Oberlaaer Strasse 235

1100 Vienna, Austria

Octapharma AB (OAB Stockholm)

Lars Forssells gata 23

11275 Stockholm, Sweden

1.3.4. Manufacturer(s) of the medical device

Gynemed GmbH & Co. KG

Wagrienring 24b

23730 Sierksdorf

GERMANY

In accordance with Council Directive 93/42/EEC, as amended, a sample from each batch of bulk and/or finished product of the human blood derivative shall be tested by a state laboratory or a laboratory designated for that purpose by a member state.

1.4. Recommended measures to the notified body

As discussed at CHMP, it would be recommended that the notified body request the following from the medical device manufacturer for device approval:

Area[1]	**Description**
Quality	See below

At the end of this consultation procedure, there were still some editorial mistakes in the dossier that remained unsolved. As they were all non-critical issues, the procedure has been concluded on day 210 with a positive opinion for the ancillary substance and the amendment of the editorial mistakes has not been further pursued. The following editorial mistakes need to be amended in the dossier and are flagged to the attention of the Notified Body:

2.3.1. The applicant should **amend the product specification of HSA concentration in the provided results (in tabular form)** in Module 3.2.P: Drug Product - 3.4.3. Final Control tests of the ancillary human blood derivative in the medical device - **Quantitative control test - Albumin concentration determination by HPLC-reversed phase (pages 25, 26 and 27)**: the product specification of HSA concentration do not correspond to the release acceptance criteria set for the concentration of human serum albumin in Module 3.2.P: Drug Product – 5. Control of Drug Product – 5.1. Specification (s) (pages 34 and 35).

For example:

- *Current*:

- GM501 PVP

Batch	*Product specification of HSA concentration*		*Measured HSA concentration by HPLC during QC for product release*
PVP-2502	~~16 ml/liter~~	~~4 g/liter~~	3.8 g/l
PVP-2503			4.3 g/l
PVP-2505			3.7 g/l

- *Proposed*:

- GM501 PVP

Batch	*Product specification of HSA concentration*	*Measured HSA concentration by HPLC during QC for product release*
PVP-2502	3.2-4.8 g/l	3.8 g/l
PVP-2503		4.3 g/l
PVP-2505		3.7 g/l

2.3.2. The applicant should **amend the product specification of HSA concentration in the media VitriStore Freeze Medium 2 and VitriStore Thaw Medium 1, 2 and 3** in Module 3.2.P: Drug Product – 5. Control of Drug Product – 5.1. Specification (s) (page 34) as well as in de **CoAs enclosed** of these media.

Product	**HSA content as per Module 3, Table 1**	**COA specification for Concentration of HSA**	**Expected HSA specification based on Table 1**
GM501 VitriStore Freeze 2	10.8 g/l	8.3-12.,4 g/l	8.6 - 13.0 g/l
GM501 VitriStore Thaw 1	18.6 g/l	14.5-21.7 g/l	14.9 - 22.3 g/l
GM501 VitriStore Thaw 2	19.3 g/l	15.2-22.8 g/l	15.4 - 23.2 g/l
GM501 VitriStore Thaw 3	19.5 g/l	15.5-23.3 g/l	15.4 - 23.2 g/l

It should be noted that the "expected HSA specification based on Table 1" of the mentioned media has to be also amended accordingly in "**Quantitative control test - Albumin concentration determination by HPLC-reversed phase (pages 25, 26 and 27)" – previous point A) - Recommended measures to the notified body.**

- *Current*:

GM501 VitriStore:

- Chemical composition
- pH: 7,20 – 7,40
- Osmolality (mOsm/kg):
  - GM501 VitriStore Pre-vitrification Medium / GM501 VitriStore Thaw Medium 4: 270 – 295 (release criteria: 270-290)
  - GM501 VitriStore Thaw Medium 1: 805-865 (release criteria: 805-850)
  - GM501 VitriStore Thaw Medium 2: 535-565
  - GM501 VitriStore Thaw Medium 3: 405-435
- Sterility by the current Ph. Eur. 2.6.1 / USP <71>: no growth
- Endotoxins by Limulus Amebocyte Lysate methodology (USP <85>): < 0,25 EU/ml
- One cell mouse Embryo Assay (blastocysts after 96h, after sequential exposure to VitriFreeze/Thaw media) ≥ 80%
- Total protein concentration (g/liter):
  - GM501 VitriStore Pre-vitrification Medium / GM501 VitriStore Thaw Medium 4: 16.0-24.0
  - GM501 VitriStore Freeze Medium 1: 12.8-19.2
  - GM501 VitriStore Freeze Medium 2: ~~8.3-12.4~~
  - GM501 VitriStore Thaw Medium 1: ~~14.5-21.7~~
  - GM501 VitriStore Thaw Medium 2: ~~15.2-22.8~~
  - GM501 VitriStore Thaw Medium 3: ~~15.5-23.3~~
- Use of Ph Eur or USP grade products if applicable

- *Proposed*:

GM501 VitriStore:

- Chemical composition
- pH: 7,20 – 7,40
- Osmolality (mOsm/kg):
  - GM501 VitriStore Pre-vitrification Medium / GM501 VitriStore Thaw Medium 4: 270 – 295 (release criteria: 270-290)
  - GM501 VitriStore Thaw Medium 1: 805-865 (release criteria: 805-850)
  - GM501 VitriStore Thaw Medium 2: 535-565
  - GM501 VitriStore Thaw Medium 3: 405-435
- Sterility by the current Ph. Eur. 2.6.1 / USP <71>: no growth
- Endotoxins by Limulus Amebocyte Lysate methodology (USP <85>): < 0,25 EU/ml
- One cell mouse Embryo Assay (blastocysts after 96h, after sequential exposure to VitriFreeze/Thaw media) ≥ 80%
- Total protein concentration (g/liter):
  - GM501 VitriStore Pre-vitrification Medium / GM501 VitriStore Thaw Medium 4: 16.0-24.0
  - GM501 VitriStore Freeze Medium 1: 12.8-19.2
  - GM501 VitriStore Freeze Medium 2: **8.6-13.0 g/l**
  - GM501 VitriStore Thaw Medium 1: **14.9-22.3 g/l**
  - GM501 VitriStore Thaw Medium 2: **15.4-23.2 g/l**
  - GM501 VitriStore Thaw Medium 3: **15.4-23.2 g/l**
- Use of Ph Eur or USP grade products if applicable

2. Scientific overview and discussion

2.1. General information

This assessment is made in the scope of the consultation procedure on an ancillary medicinal substance in medical devices with the EMA as a consequence of the new Medical Device Regulation 2017/745 (MDR) and Medical Device Coordination Group (MDCG) guidance document 2020-12. In the past, the Committee for

Medicinal Products for Human Use (CHMP) granted a positive opinion on the use of both sources of human serum albumin, i.e., Plasbumin 25% (Grifols) and Albunorm (Octapharma), in Gynemed GmbH HSA-containing ART media but based on the MDR and guidance document 2020-12 a new consultation must be performed.

Table 1 - General description of Gynemed GmbH & Co. KG HSA-containing ART media

General description:

Medical device manufacturer	Gynemed GmbH & Co. KG
Notified Body	BSI Group - The Netherlands BV
Medicinal substance manufacturer	1/ Grifols manufacturing sites: Grifols Therapeutics (GT) 8368 US 70 Business Hwy. West Clayton, North Carolina 27520 Instituto Grifols, S.A. C/Can Guasc,2 08150 Parets del Vallès Barcelona, Spain 2/ Octapharma: manufacturing sites: Octapharma Pharmazeutika ProduktionsgesmbH Oberlaaer Strasse 235 1100 Vienna – Austria (performs manufacturing and packaging of albumin) Octapharma AB, Lars Forssells gata 23 11275 Stockholm – Sweden (performs manufacturing of albumin) Octapharma GmbH Otto-Reuter-Strase 3 06847 Dessau - Germany (performs packaging of albumin manufactured at site in Sweden) Octapharam AG Siedenstrasse 2 8853 Lachen -Switzerland (performs import, distribution and export of medicinal products).

Invented name of medical device	Gynemed GmbH & Co. KG. HSA-containing ART media: 1. GM501 PVP 2. GM501 Hyaluronidase 3. GM501 SpermStore 4. GM501 VitriStore Freeze / Thaw: - GM501 VitriStore Pre-Vitrification Medium - GM501 VitriStore Freeze Medium 1 - GM501 VitriStore Freeze Medium 2 - GM501 VitriStore Thaw Medium 1 - GM501 VitriStore Thaw Medium 2 - GM501 VitriStore Thaw Medium 3 - GM501 VitriStore Thaw Medium 4 5. GM501 GentleVit Freeze / Thaw: - GM501 GentleVit Pre-Vitrification Medium - GM501 GentleVit Freeze Medium 1 - GM501 GentleVit Freeze Medium 2 - GM501 GentleVit Freeze Medium 3 - GM501 GentleVit Freeze Medium 4 - GM501 GentleVit Freeze Medium 5 - GM501 GentleVit Thaw Medium 1 - GM501 GentleVit Thaw Medium 2 - GM501 GentleVit Thaw Medium 3 - GM501 GentleVit Thaw Medium 4 - GM501 GentleVit Thaw Medium 5 - GM501 GentleVit Thaw Medium 6 6. GM501 Washing Media: - GM501 Wash - GM501 Wash with phenol red and gentamicin - GM501 SpermActive - GM501 SpermAir 7. GM501 Cult Media: - GM501 Cult with gentamicin - GM501 Cult with phenol red and gentamicin
Ancillary medicinal substance	Human Albumin Solution
Strength of the ancillary medicinal substance	25% w/v (250 g/L)
Trade name of medicinal substance	1/Grifols: Plasbumin 25% (alternative name: Albumin (human) 25%) 2/Octapharma: Albunorm (alternative name Albumin (human) 25%)
Major amendment to dossier number:	EMEA/H/D/2518 and EMA/ EMA/H/D/002518/II/0001

Gynemed GmbH & Co. KG HSA-containing ART media are a range of media products designed for use in Assisted Reproduction Technologies (ART). Table 1 provides an overview of all Gynemed GmbH & Co. KG HSA-containing ART media. They have direct physical contact with human gametes or embryos for the purposes of preparation, maintenance, transfer or storage. During intrauterine insemination or embryo transfer, the media come in contact with the uterus mucosal membrane. The intended uses of the media depend on the type of medium. The sterile media are supplied in sterile, labelled bottles which are placed in boxes along with a package insert.

Gynemed GmbH & Co. KG HSA-containing ART media consist of various compositions of physiological salts, nutritional and energy substances and buffer systems. To enhance specific properties, some media also contain specific medium supplements, cryoprotectants or antibiotics. Since all media contain human albumin solution (as an ancillary substance), they are considered as Class III medical devices according to Rule 14 of the Medical Device Regulation 2017/745

2.2. Quality documentation

Inspection status

Valid certificates of Good Manufacturing Practices (GMP) compliance have been provided for manufacturers and release testing sites of the ancillary substance except for Grifols Deutschland GmbH Octapharma S.A.S. (France) and Octapharma Produktionsgesellschaft Deutschland mbH (Germany). Therefore, major objections have been raised requesting clarification of the responsibilities and GMP status of the sites, which were adequately addressed by the Applicant during the procedure, by confirming that these sites are not involved in the manufacturing of Albunorm 25% or Plasbumin 25%.

2.2.1. For the ancillary medicinal substance or the ancillary human blood derivative itself

Gynemed GmbH & Co. KG HSA-containing ART media (hereinafter referred as "Gynemed") are a range of media products designed for the use in Assisted Reproductive Technologies (ART). The intended use of Gynemed media depends on the type of medium. Since *all media contain human albumin (as an ancillary substance)*, they are considered as Class III medical devices according to Rule 14 of the Medical Device Regulation 2017/745.

The ancillary substance under evaluation in this procedure is Human Serum Albumin (HSA). Two alternative medicinal products can be incorporated into Gynemed as ancillary HSA and the applicant has confirmed that both medicinal products hold a Marketing Authorisation (MA) in the EU:

- **Albunorm 25%**, supplied by Octapharma.
- **Plasbumin 25%**, supplied by Grifols.

Albunorm 25% is registered in Austria with a registration number 2-00378. Plasbumin 25% is registered in Germany with a registration number 10537a/96.

For Albunorm 25% (Octapharma), Vienna and Stockholm manufacturing sites are involved in the manufacturing of Albunorm 25%:

- Octapharma Pharmazeutika ProduktionsgesmbHIG (OPG Vienna) - Oberlaaer Strasse 235; 1100 Vienna, Austria
- Octapharma AB (OAB Stockholm) - Lars Forssells gata 23; 11275 Stockholm, Sweden

The functions performed by OPG Vienna and OAB Stockholm are the same: production from plasma to final product, visual inspection, labelling, packaging and batch release.

For Plasbumin 25% (Grifols): it is manufactured by Grifols Therapeutics (GT) and Instituto Grifols Barcelona (IG) is responsible of the release.

- Grifols Therapeutics LLC (GT) - 8368 US 70 Business Hwy. West; Clayton, North Carolina 27520, USA
    - *GT* – responsible for the manufacture of the AS (bulk), the aseptic filling, the manufacturing and the analytical testing of the DP (filled, unlabelled vials)
- Instituto Grifols, S.A. (IG) - C/Can Guasc,2, 08150 Parets del Vallès; Barcelona, Spain
    - *IG* – responsible for the sterility and quality control of the finished product as well as for the batch release of the finished product for the European Union (EU) market

The following summary quality aspects are noted for both sources of albumin:

- Both albumin medicinal products are in compliance with Ph. Eur. monograph 01/2022:0255. for Human Albumin Solution;
- Both are confirmed as marketed as medicinal products within the European Union:
    - Albunorm 25%, supplied by Octapharma, is registered in Austria with a registration number 2-00378;
    - Plasbumin 25%, supplied by Grifols, is registered in Germany with a registration number 10537a/96.
- Plasma Master File certificates have been provided for both the Octapharma and Grifols albumins.
- Both are subject to OCABR, for which representative OCABR certificates have been provided.

2.2.1.1. Active substance

The information comprising from collection of human plasma to the preparation of plasma pools is evaluated in a separate and independent dossier that is certified by European Medicines Agency (EMA) through the PMF certification procedure. For Plasbumin 25% and Albunorm 25% the EMA PMF certificates have been submitted (PMF certificates number EMEA/H/PMF/000008/05/AU/034/G held by Octapharma Pharmazeutika ProduktionsgesmbH Oberlaaer Strasse 235 A-1100 Vienna Austria and PMF number EMEA/H/PMF/000002/04/AU/041/G held by Institute Grifols, S.A. Poligono Levante, c/Can Guasch, 2 08150 Parets del Valle Barcelona, Spain, respectively).

The manufacturing process of the human albumin is a continuous process, although both manufacturers in the dossiers refer to the bulk solution as the active substance (AS) and to the human albumin 25% in final containers as the finished product (FP).

2.2.1.1.1. Nomenclature and structure

For both Plasbumin 25% and Albunorm 25% the active substance human albumin has been defined as the final sterile bulk, which contains the appropriate concentration of the HSA protein prior to aseptic filling. Information is also included regarding "Nomenclature", "Structural Formula" and "General Properties". The data provided in this section is considered adequate.

2.2.1.1.2. Manufacture, characterisation and process controls

Section "Manufacture" has been provided for both ancillary substances (Plasbumin 25% and Albunorm 25%). The GMP compliance of the manufacturing sites has been assessed and clarified during the procedure and no GMP compliance issues for these sites were identified.

All used plasma complies with the current version of the corresponding approved PMF.

The manufacturing processes have been described adequately, and complete flow charts have been enclosed, detailing all the fractionation and purification steps from the frozen plasma to the finished product. Information about the validation of the processes has been provided, as well as the control of raw materials and the in-process controls of the manufacturing processes, and they are overall acceptable.

Specifically, regarding Plasbumin 25%, the manufacture of the active substance involves cold ethanol fractionation of the pooled plasma to the final Fraction V paste step which is followed by purification of the suspension of the Fraction V paste to the sterile bulk. The finished product is manufactured by aseptically filling the sterile bulk into sterile bottles, which are then pasteurized for 10 to 11 hours at 59.5 to 60.5°C within 24 hours after completion of filling. Final containers are incubated at 20 to 35°C for NLT 14 days and then stored at NMT 30°C.

For Albunorm 25%, a full description of the manufacture by ethanol fractionation and followed by final container pasteurisation has been set out. Full details of the manufacture including narrative description and detailed process flow diagram in process controls, controls of critical steps and intermediates, and validation of the manufacture.

The responsibilities for the entities involved in the different steps of the manufacturing process have been also indicated for both Plasbumin 25% and Albunorm 25%. Valid GMP certificates for these sites were submitted.

2.2.1.1.3. Specifications

In relation to Plasbumin 25%, the AS is tested for protein composition by the validated method Capillary Zone Electrophoresis (CZE). The specification for the bulk has been set at not less than 96% albumin. Regarding Albunorm 25%, its dossier contains the description of the analytical methods and validation of analytical procedures used for the quality control of the bulk active substance. Specifications of the AS have also been provided. The data provided in this section is considered adequate.

Container closure system

The bulk of Plasbumin 25%, is stored in stainless steel tanks, with various sizes and the bulk of Albunorm 25% can be stored both in stainless steel tanks and polyethylene (PE) containers. Adequate description of all containers and supporting data of the PE containers have been enclosed. The data provided in this section is considered sufficient.

2.2.1.1.4. Stability

The shelf-life of Plasbumin 25% and Albunorm 25% bulk (DS) is 30 and 28 days, respectively, when stored at +5°C under the proposed storage conditions. These shelf-lives have been defined based on the results obtained in real-time stability studies. The data provided in this section is considered adequate.

2.2.1.2. Finished product

2.2.1.2.1. Description of the product and pharmaceutical development

Composition

The composition of both FP is presented in tabular form. Plasbumin 25%, FP is a clear, slightly viscous pale yellow, amber or green coloured liquid that is administered intravenously. It is available in 50 and 100 mL clear glass vials (Ph. Eur./USP type II glass). The composition includes excipients N-Acetyl-DL-tryptophan and Sodium Caprylate which meet the requirements of the Ph. Eur., as described in table below:

Table 2 - Composition of finished product Plasbumin 25%

Size	Active Ingredients	Other Ingredients			
	Albumin[a]	Sodium Caprylate	N-Acetyl-DL-Tryptophan	Sodium[b]	Water for Injection (WFI)
mL	0.25 g	0.00332 g	0.00493 g	0.00333 g	q.s. to 1 mL
Function	Active ingredient	Stabilizer	Stabilizer	Tonicity	Solvent
Reference to Standard	EP	NF/EP	EP	----[c]	USP/EP

[a] Not less than 95% of the protein has the electrophoretic mobility of albumin.
[b] Value represents sodium ion concentration from all sources.
[c] Complies with specifications.

In relation to Albunorm 25%, FP is dispensed in colourless 70 ml and 100 ml glass bottles of glass type II (Ph. Eur.). The composition of Albunorm 25% is detailed in the table below and includes N-acetyl-DL-tryptophan and Caprylic acid as stabilisers which meet the requirements of the Ph. Eur.

Table 3 - Composition of finished product Albunorm 25%

Name of Active Ingredients	Quantity per 1000 ml	Function	Reference to Standards
Plasma proteins with at least 96% human albumin	250 g	Active Ingredients	Internal
Name of Excipients	**Quantity per 1000 ml**	**Function**	**Reference to Standards**
Sodium[1]	144-160 mmol	osmotic and electrolyt component	Ph. Eur
N-acetyl-DL-tryptophan	16-24 mmol	Stabiliser	Ph. Eur.
Caprylic acid	16-24 mmol	Stabiliser	Ph. Eur.
Water for injections	ad 1000 ml	Solvent	Ph. Eur.
Name of other Components	**Quantity per 1000 ml**	**Function**	**Reference to Standards**
Potassium[2]	≤ 12.5 mmol	osmotic and electrolyt component	Ph. Eur

[1]Sodium is added to the solution as sodium chloride and also as part of different buffer solutions. The quantity of sodium chloride varies depending on the sodium content on the solution in order to adjust to the requested final concentration of 144-160 mmol sodium per l protein solution.
[2]Potassium is a component of the human plasma starting material and not actively added as excipient.

2.2.1.2.2. Manufacture of the product and process controls

For both FPs, information about the manufacturers has been enclosed. The manufacturing process and the controls have been sufficiently described. The flow charts for the manufacturing of the FPs are also provided. Information about the validation of the processes is included and it is considered complete and suitable. The data provided in this section is considered sufficient.

2.2.1.2.3. Control of excipients

Adequate descriptions of the excipients have been provided.

Regarding Plasbumin 25% FP, the excipients are N-Acetyl-DL-Tryptophan and Sodium Caprylate. It is stated that the specifications set for these excipients follow those set out in the current version of Ph. Eur. and USP.

In relation to Albunorm 25% FP, the excipients are N-Acetyl-DL-Tryptophan, Octanoic Acid, Sodium Chloride and Water for Injections. All excipients are of Ph. Eur. quality and tested according to Ph. Eur. methods.

2.2.1.2.4. Product specifications

Regarding Plasbumin 25% FP shelf-life and release specifications are provided (table below) and are in accordance with the current Ph. Eur.

Table 4 - Plasbumin 25% FP shelf-life and release specifications

Test	Specification	Reference	Method
N-Acetyl-DL- Tryptophan	0.07 to 0.09 mmol/g protein	Ph. Eur.	IG_MA-000197A_ING
Aluminum	≤ 200 µg/L	Ph. Eur.	IG_MA-000324A_ING
	≤ 100 µg/L*	Grifols	
Appearance	Clear, slightly viscous, pale yellow to amber or green	Ph. Eur.	IG_MA-000003B_ING
Sodium Caprylate	0.07 to 0.09 mmol/g protein	USP	IG_MA-000198A_ING
Citrate	≤ 0.1 mmol/L	Grifols	IG_MA-000750_ING
Fill Volume	Meets minimum fill volume	USP	IG_MA-000115A_ING
Haem (O.D. 403 nm, 1% w/V)	≤ 0.15 A	Ph. Eur.	IG_MA-000006A_ING
pH of 1% Protein Solution	6.7 to 7.3	Ph. Eur.	IG_MA-000004A_ING
Polymers and Aggregates	≤ 5%	Ph. Eur.	IG_MA-000158A_ING
Potassium	≤ 0.05 mmol/g protein	Ph. Eur.	IG_MA-000005A_ING
Prekallikrein Activator (PKA)	≤ 35 IU/mL	Ph. Eur.	IG_MA-000297C_ING
Product Identity (Grabar-Williams)	Main component is albumin	Ph. Eur.	IG_MA-000266A_ING
Total Protein	23.75 to 26.25%	Ph. Eur.	IG_MA-000007A_ING
Purity (AME)	≥ 95% Albumin	Ph. Eur.	IG_MA-000009B_ING
Pyrogen, EP	Must comply	Ph. Eur.	IG_MA-000011A_ING
Sodium	130 to 160 mmol/L	USP (1)	IG_MA-000005A_ING
Sterility	No growth	Ph. Eur.	IG_MA-000012C_ING

(1) Ph. Eur. Specification: Maximum 160 mmol/L

European Pharmacopoeia (Ph. Eur.): The current edition of the European Pharmacopoeia will be used.
United States Pharmacopeia (USP): The current edition of the USP will be used.

In relation to Albunorm 25% FP shelf-life and release specifications are provided (table below) and are in accordance with the current Ph. Eur.

Table 5 - Albunorm 25% FP shelf-life and release specifications

Characters	Ph.Eur.	A clear, slightly viscous liquid; it is almost colourless, yellow, amber or green.
Identification		
Immunoelectrophoresis:	Ph.Eur.	Strong albumin precipitation band with anti-human-serum.
Tests		
pH value:	Ph.Eur. (2.2.3)	6.7 - 7.3
Albunorm 4% Total protein:	Ph.Eur. (Biuret) (2.5.33)	3.8 - 4.2 % (w/v)
Albunorm 5% Total protein:	Ph.Eur. (Biuret) (2.5.33)	4.75 - 5.25 % (w/v)
Albunorm 20% Total protein	Ph.Eur. (Biuret) (2.5.33)	19.0 - 21.0 % (w/v)
Albunorm 25% Total protein	Ph.Eur. (Biuret) (2.5.33)	23.8 - 26.2% (w/v)
Protein composition:	Electrophoresis	≥ 96 % Albumin
Molecular size distribution: (Polymers and aggregates)	Ph.Eur. (2.2.29)	≤ 10% of the total chromatogram area (corresponds to about 5% of polymers and aggregates)
Haem content:	Ph.Eur. (2.2.25)	Absorption: ≤ 0.150
Prekallikrein activator:	Ph.Eur. (2.6.15)	≤ 35 IU/ml
Aluminium:	Ph.Eur. (2.2.23)	≤ 200 µg/l (ppb)
Albunorm 4% Potassium:	Ph.Eur. (2.2.22)	≤ 2.0 mmol/l
Albunorm 5% Potassium:	Ph.Eur. (2.2.22)	≤ 2.5 mmol/l
Albunorm 20% Potassium:	Ph.Eur. (2.2.22)	≤ 10 mmol/l
Albunorm 25% Potassium:	Ph.Eur. (2.2.22)	≤ 12.5 mmol/l
Sodium:	Ph.Eur. (2.2.22)	144 - 160 mmol/l
Sterility:	Ph.Eur. (2.6.1)	Sterile
Albunorm 25% Endotoxin :	Ph.Eur. (2.6.14)	< 1.7 IU/ml

A nitrosamines risk evaluation performed in accordance with Questions and answers on "Information on nitrosamines for marketing authorisation holders" (EMA/409815/2020) and Nitrosamine Impurities - Final

Outcome of Article 5(3) (EMA/369136/2020) was missing and a major objection (MO) was raised. As response, evaluation reports of Nitrosamine Risk to 25% Albumins, carried out by the manufacturers of these ancillary substances, Grifols and Octapharma, have been enclosed. For both, no possible causes are identified within the manufacturing processes of Albumin that might lead to a safety concern for the presence of nitrosamine impurities in the final product. In addition, a Risk Assessment Report of the risk of nitrosamines formation in the medical device Gynemed is provided.

Based on overall information provided, it is concluded that the nitrosamine risk foreseen from the incorporation of the ancillary substance into the device can be considered negligible. The MO was considered solved.

2.2.1.2.5. Container closure system

Plasbumin 25% is stored in of Type II Clear Glass Bottles, West 1821 black, halo butyl isoprene rubber blend stoppers and West 4432/50 chlorobutyl gray 20 mm stopper. The glass bottles meet the requirements for the USP and Ph. Eur. monographs for bottles and the stoppers meet the requirements for the Ph. Eur. monograph for stoppers.

Albunorm 25% is supplied in bottles of glass type II (Ph. Eur.) with different filling sizes (70, 100, 250 and 500 ml). The bottles are closed with bromobutyl-stoppers 32 mm of type I (Ph. Eur.) and sealed with a flip-off cap. The manufacturers of each component of the container closure system have been indicated and specifications, technical drawings and certificates of analysis are enclosed. All components are latex-free.

The data provided in this section is considered sufficient and adequate.

2.2.1.2.6. Stability of the product

For both products, the approved shelf-life under the specified storage conditions is 36 months when stored in the final container. The stability data provided in both dossiers support the approved shelf-life. Moreover, the post-approval stability protocol and stability commitments have also been enclosed in each dossier.

2.2.1.2.7. Adventitious agents

For both products, viral validation studies were performed to evaluate the capacity of the manufacturing process to remove/inactivate virus.

In relation to Plasbumin 25%, a detailed viral safety discussion has been provided which evaluates the scaled-down models of the Precipitation of Fraction II+III and Precipitation of Fraction IV steps respectively. No scale-down model was required to evaluate the Pasteurisation step. The choice of viruses' studied have been sufficiently justified, whereby HIV-1 is selected as it is a relevant bloodborne pathogen, BVDV to model hepatitis C virus, PRV as a surrogate for large, enveloped DNA viruses and can be used to model hepatitis B virus for which there is no practicable assay system. Additionally, Reo3 was selected to model non-enveloped viruses, HAV for relevant non-enveloped virus and PPV as a surrogate for human parvovirus B19.

Furthermore, WNV was evaluated for the pasteurization step while the model non-enveloped virus EMCV was evaluated for the precipitation of Fraction IV step only. The log10 virus clearance capacities are summarised in Table 2 and demonstrate a high margin of safety with respect to the transmission of enveloped and non-enveloped viruses.

The overall Virus Clearance Capacity (Log10) of Plasbumin 25% manufacturing process is summarized in the table below:

Table 6 - Virus Clearance Capacity (Log10) of Plasbumin 25% manufacturing process

Process Step	Enveloped Viruses			Non-enveloped Viruses		
	HIV-1	BVDV	PRV	Reo3	HAV	PPV
Precipitation of Fraction II+III	3.4	3.5	3.9	≥2.1	1.4	1.0
Precipitation of Fraction IV[a]	≥4.3	≥4.1	≥3.9	≥4.4	3.9	4.6
Pasteurization[b]	≥5.9	≥5.2	≥4.8	5.6	4.4	1.6
Overall Clearance Capacity	**≥13.6**	**≥12.8**	**≥12.6**	**≥12.1**	**9.7**	**7.2**

[a] EMCV was also evaluated for the Precipitation of Fraction IV step. The virus clearance capacity (log_{10}) was 3.7.

[b] WNV was also evaluated for the Pasteurization step. The virus clearance capacity (log_{10}) was ≥6.7.

No animal-derived materials are used in the manufacture of this albumin. The Transmissible Spongiform Encephalopathies (TSE) clearance capacity has also been evaluated using bench scale models whereby process-intermediates were spiked with TSE-infected material. For the Pooled Plasma to Effluence IV-1 Fractionation steps, the was a greater than 7 log $_{10}$ reduction of TSE Infectivity Clearance by Bioassay and greater than log 4.7 clearance of protease-resistant form of the pathogenic prion protein measured by Western Blot thus supporting that there is a very low risk of TSE transmission by the use of albumin.

Sufficient information has been provided with respect to viral safety and TSE infectivity.

Regarding Albunorm 25%, Octapharma has provided a Pathogen Safety Statement and a summary viral safety discussion which evaluates clearance results (as logarithmic reduction factors) for both the cold ethanol precipitation and pasteurisation steps using a range of enveloped and non-enveloped model virus and hamster-adapted scrapie strain 263K as a model for prions.

A suitable range of model viruses have been used for the viral clearance study.

The overall pathogen clearance results (Log10) of Albunorm 25% manufacturing process are summarized in the table below:

Table 7 - Pathogen clearance results (Log10) of Albunorm 25% manufacturing process

Pathogen human	HIV-1/2	HBV	HCV, WNV	HAV	B19V	Prion
(Relevant model)	(HIV-1)	(PRV)	(SBV)	(MEV)	(PPV)	(HAS 263K)
Manufacturing step	Logarithmic reduction factor (LRF) [log_{10}]					
Cold ethanol precipitation	4.98	≥ 5.70	5.89	2.88	3.52	≥ 3.86
Final container pasteurization	≥ 7.23	≥ 8.67	≥ 8.79	3.70	2.25	n/a
Global reduction factor	**≥ 12.21**	**≥ 14.37**	**≥ 14.68**	**6.58**	**5.77**	**≥ 3.86**

HIV-1: Human immunodeficiency virus type 1, model for HIV type 1 and HIV type 2
PRV: Pseudorabies virus, model for e.g., hepatitis B virus (HBV)
SBV: Sindbis virus, model for e.g., hepatitis C virus (HCV) and West Nile virus (WNV)
MEV: Mouse encephalomyelitis virus, model for hepatitis A virus (HAV)
PPV: Porcine parvovirus, model for human parvovirus B19 (B19V)
HAS 263K: hamster-adapted scrapie strain 263K, model for prions
n/a: not applicable
≥: pathogen reduction below the detection limit

With respect to evaluation of TSE (vCJD) risk, the worst-case conditions are stated as employed. Applying the CPMP/ICH/295/95 formulae for calculation of the estimated prion particles per vial Albunorm 25 %, the Octapharma statement contends that as many as 151,222 contaminated Albunorm 25 % 100 mL vials are needed before one patient would possibly contract vCJD. This corresponds to 3.8 tons of albumin or 32 full Albunorm batches. As most patients are treated only once or twice in lifetime with Albunorm, this amount of albumin corresponds to 63,009-126,018 lifetime treatments (30 gr/70 kg BW x 1-2) and therefore is considered as low risk.

One batch of Albumin is manufactured from an equivalent of 800-4,200 kg plasma. Plasma donations of 250 mL (recovered plasma) or 1,183 mL (source plasma) are used. Based on the Albumin batch size of 4,200 kg, the maximum number of donations in one batch is 16,800 (250 mL units) or 3,550 (1,183 mL units), respectively. All plasma units used are tested by NAT on a minipool basis by the collection centers or Octapharma. The minipool size is in general smaller when the testing is performed by the collection centers (x4-512) compared to Octapharma in-house testing (x480).

Albunorm 25% is demonstrated to be of low risk with respect to viral and TSE safety.

The results obtained using model viruses demonstrate a high safety level. The data provided are considered adequate and show that the manufacturing processes for Albumin from both suppliers have sufficient capacity to ensure elimination/inactivation of a wide range of potential contaminant virus and ensure viral safety when products are used as per their indications approved in the Marketing Authorisations (MA) of the albumin products.

Overall, the data provided in this section is considered sufficient and adequate. However, particular attention should be paid to the risk of B19 Human Parvovirus transmission when incorporating HSA into ART media systems, as the intended use differs from the indications approved in the MA of the albumin products. Severe anaemia and non-immune hydrops fetalis can occur in foetuses infected by B19 Human Parvovirus. Nucleic acid testing (NAT) screening for exclusion of high titre donations can significantly reduce the contamination of plasma pools thereby reducing the risk for transmissions and resulting potential complications.

In this sense, a Major Objection (MO) was raised during the procedure. As response, Grifols has submitted a statement, in regard to the plasma manufacturing pools used in the manufacture of Plasbumin 25%. It is declared that "the plasma pools are tested for B19 virus DNA. These corresponding limit for B19 DNA in the plasma manufacturing pools tested does not exceed 10^4 IU/ml".

Regarding Albunorm 25%, manufactured by Octapharma, a Certificate of Analysis for one batch of Albunorm 25% manufactured in September, 2024 is enclosed, where it is indicated that "*It is certified that the plasma pool was found [….] with less than 10^4 IU/ml for Parvo B-19 genome*". However, no specific reference is made to B19 NAT testing in all plasma pools used for Albumin 25% as ancillary substance nor to the specific acceptance limit applied for these pools in the B19 NAT testing. So, the information provided for Albunorm 25% did not allow to conclude that the potential transmission of Parvovirus B19V to foetuses is adequately prevented for this ancillary substance manufactured by Octapharma. Consequently, a follow-up question (MO) has been raised. To address this MO in relation to Albunorm 25%, a statement has been submitted and it is declared that "all plasma pools […] are Parvo-B19 NAT tested with a limit less than 10^4 IU/ml for Parvo B-19 genome".

Thus, taking into account the statements submitted by both Grifols and Octapharma, it is concluded that an adequate safety margin for B19V is in place for ancillary substances and it is considered acceptable.

2.2.2. For the ancillary medicinal substance or the ancillary human blood derivative as incorporated in the medical device

2.2.2.1. Qualitative and Quantitative particular of the constituents

Gynemed GmbH & Co. KG HSA-containing ART media is a range of media each of which contain Human Albumin Serum 25% w/v (250g/L). The media come in direct physical contact with human gametes or embryos and/or uterus mucosal membrane during intrauterine insemination/embryo transfer.

Specifically, Gynemed consists of 28 different solutions that are combined into 7 types of media for ART (GM501 VitriStore Freeze/Thaw; GM501 GentleVit Freeze/Thaw; GM501 PVP; GM501 Hyaluronidase; GM501 Cult media and GM501 Washing media), all of which contain HSA as ancillary substance. Additionally, the Gynemed media contain various compositions of physiological salts, nutritional and energy substances, buffer systems combined with the HSA as an ancillary substance. Media for cryopreservation of spermatozoa and/or embryos also contain cryoprotectants. Antibiotics are added to certain cell culture media to reduce risk of potential microbial infection during culture. Excipients in the formulations are ethylenediaminetetraacetic acid disodium salt dihydrate (EDTA), phenol red and gentamicin sulphate.

The exact qualitative and quantitative media compositions for each of the seven types of ART media have been provided. The ancillary human blood derivative that takes part of the media is HSA which is mixed in the media homogenously. The amount of human albumin used in each of the devices/media is dependent on the type of medium and ranges from 0.16% to 8% (v/v) corresponding to a range of 0.4 g/l and 20 g/l human serum albumin respectively in the product. The specific quantity of human serum albumin in each media and its concentration is detailed in the information provided.

The submitted dossier provides a summary with respect to each of the devices, their intended purpose (pH and osmotic regulation, stabilization of cell membrane, nutrient and carrier of growth promoting substance, aid in

fertilization process, scavenger, surfactant and cryoprotectant), HSA concentration (% v/v) and final albumin concentration (% v/v), package size and unopened shelf-life.

The full compositions of each individual device and a summary of the amount of human albumin solution in Gynemed GmbH & Co. KG HSA containing ART media products per product are provided (table below).

A table which declares the final amount of human albumin in each medium is provided. The amount of albumin on the final labelling and on the IFU should correspond with the quantities declared in this table. In addition, the information in this table should be the basis for the release specifications for HSA content for each medical device.

Table 8 - Amount of human albumin solution in Gynemed GmbH & Co. KG HSA containing ART media products per product

Table 1:

Name and type of media	Amount of Human Albumin Solution in the media	Amount of human albumin in the media
GM501 SpermStore	15.9 ml/l	4.0 g/l
GM501 VitriStore Freeze/Thaw:		
GM501 VitriStore Pre-Vitrification (= GM501 VitriStore Thaw Medium 4)	80.0 ml/l	20.0 g/l
GM501 VitriStore Freeze Medium 1	64.0 ml/l	16.0 g/l
GM501 VitriStore Freeze Medium 2	48.0 ml/l	10.8 g/l
GM501 VitriStore Thaw Medium 1	80.0 ml/l	18.6 g/l
GM501 VitriStore Thaw Medium 2	80.0 ml/l	19.3 g/l
GM501 VitriStore Thaw Medium 3	80.0 ml/l	19.5 g/l
GM501 GentleVit Freeze/Thaw:		
GM501 GentleVit Pre-Vitrification (= GM501 GentleVit Thaw Medium 6)	80.0 ml/l	20.0 g/l
GM501 GentleVit Freeze Medium 1	78.0 ml/l	19.5 g/l
GM501 GentleVit Freeze Medium 2	76.0 ml/l	19.0 g/l
GM501 GentleVit Freeze Medium 3	72.0 ml/l	18.0 g/l
GM501 GentleVit Freeze Medium 4	64.0 ml/l	16.0 g/l
GM501 GentleVit Freeze Medium 5	43.2 ml/l	10.8 g/l
GM501 GentleVit Thaw Medium 1	69.6 ml/l	17.4 g/l
GM501 GentleVit Thaw Medium 2	79.9 ml/l	18.0 g/l
GM501 GentleVit Thaw Medium 3	74.4 ml/l	18.6 g/l
GM501 GentleVit Thaw Medium 4	77.1 ml/l	19.3 g/l
GM501 GentleVit Thaw Medium 5	78.6 ml/l	19.6 g/l
GM501 PVP	16.0 ml/l	4.0 g/l
GM501 Hyaluronidase	16.0 ml/l	4.0 g/l
GM501 Cult media:		
GM501 Cult G	40.0 ml/l	10.0 g/l
GM501 Cult PRG	40.0 ml/l	10.0 g/l
GM501 Washing media:		
GM501 Wash	20.0 ml/l	5.0 g/l
GM501 Wash PRG	20.0 ml/l	5.0 g/l
GM501 SpermActive	20.0 ml/l	5.0 g/l
GM501 SpermAir	20.0 ml/l	5.0 g/l

It is noted that:

a) From the information supplied in Module 1, based on 25% albumin content of the Human Albumin Solution used in manufacturing, the applicant has corrected a typographical error in the table, to confirm that GM501 GentleVit Thaw Medium 1 and GM501 GentleVit Thaw Medium 3, contain Albumin 1.75% v/v and Albumin 1.85% v/v respectively. All devices are now presented as containing 25% v/v albumin.

b) For the Module 3, Table 1, which is derived from the medium compositions, the Applicant was requested to provide clarification regarding the declared final amount of human albumin in some of the media based on the albumin being added as a 25% Human Albumin Solution. The applicant has explained that the "inconsistency is due to the theoretical volume included in one liter of medium versus the actual volume taken into account when all raw materials are added (i.e. a relatively high proportion (volume) of sucrose is added to these products)". It is understood from this response, that different formulations will have different final densities resulting in differences in the final declarations stated in terms of g/l. Therefore, the declared contact of albumin was updated in Table 1, Module 3 for the following products:

- GM501 VitriStore Freeze Medium 2 declared as 10.8 g/L;
- GM501 VitriStore Thaw Medium 1, 2 and 3 as 16.7 g/l, 19.3 g/l and 19.5 g/l respectively; and
- GM501 GentleVit Thaw Medium 2 as 18.0 g/L

In addition, the applicant updated the table to one decimal place for all entries and now includes GM501 SpermActive and GM501 SpermAir for completion.

However, while the final content of albumin for VitriStore Freeze Medium 2 and VitriStore Thaw Medium 1, 2 and 3 have been clarified, release specifications do not match the 80-120% approach of the declared content as summarised in the table below. Therefore, it will be recommended to the notified body to revise these release specifications accordingly (see section 7. Recommended measures to the notified body).

Product	HSA content as per Module 3, Table 1	COA specification for Concentration of HSA	Expected HSA specification based on Table 1
GM501 VitriStore Freeze 2	10.8 g/l	8.3-12.,4 g/l	8.6 - 13.0 g/l
GM501 VitriStore Thaw 1	18.6 g/l	14.5-21.7 g/l	14.9 - 22.3 g/l
GM501 VitriStore Thaw 2	19.3 g/l	15.2-22.8 g/l	15.4 - 23.2 g/l
GM501 VitriStore Thaw 3	19.5 g/l	15.5-23.3 g/l	15.4 - 23.2 g/l

2.2.2.2. Description of method of manufacture

The manufacturers involved in the manufacturing process of Gynemed as well as their responsibilities have been indicated in sufficient detail.

All specific steps that are followed for the Human Albumin Solution since its incorporation to the manufacturing process of Gynemed are detailed. The process is validated and the description of the different steps of the process, including the critical steps and validation protocols, was provided. The applicant has provided the process controls for each of the specific media. These include pH, osmolality, bioburden (alert level and action level), and viscosity for GM501 PVP only. Some information about the types of minor deviations which are regarded as acceptable are provided.

The manufacturing process is considered adequate.

2.2.2.3. Control of starting materials

The ancillary substances, Plasbumin 25% and Albunorm 25% are defined as raw material for use in Gynemed media. Regarding the process preceding the use of human albumin solution in Gynemed, the steps carried out with the incoming bottles are detailed. The release criteria that have to meet each new batch of Human Albumin Solution are adequately described. These include EMA approved PMF certificate, CoA / EC official control authority batch release certificate, check of batch number, check of expiry date, Statement of the Official Medicine Control Laboratory, check of Temperature log of shipment, Mouse embryo assay (MEA), endotoxin test (LAL test) and albumin concentration measurement (High Performance Liquid Chromatography (HPLC)-Reversed Phase).

In this sense, the current EMA PMF Certificates of both Grifols and Octapharma are provided, as well as representative EU/EEA Official Control Authority Batch Release (OCABR) Certificates for both Plasbumin 25% and Albunorm 25%.

2.2.2.4. Control test carried out at intermediate stages of the manufacturing process of the medical device

The control tests carried out during manufacturing of Gynemed media are sufficiently described. As the media are manufactured in a continuous manner, no measurement of human albumin content is made until the final media is obtained. It is stated that the tests carried out in the human blood derivative are performed immediately before aseptic filtration and include determination of pH, osmolality, density and/or viscosity if applicable. The analytical procedures are properly described in the dossier as well as their validation.

2.2.2.5. Final control tests of the ancillary medicinal substance or the ancillary human blood derivative in the medical device.

Information about the analytical procedures, their validation as well as the specifications of the device(s) is provided.

Three final control tests are performed on the device: Albumin concentration determination by HPLC-reversed phase, Mouse Embryo Assay (MEA) and Human Sperm Survival Assay (HSSA)/Sperm Survival Test (SST).

The validation of the HPLC method to quantify the albumin content is a publication on the "Development and validation of a high-performance liquid chromatography (HPLC) method for the determination of human serum albumin (HSA) in medical devices". This publication demonstrates that the method is fit for purpose. The applicant has confirmed that this validation study has been performed in accordance with the guidelines of the CDER and the ICH.

The validation study published in the abovementioned paper was aimed at validating the reverse phase (RP) high-performance liquid chromatography (HPLC) method used to assess HSA content in ART-related media. Moreover, the applicant has clarified and confirmed that some of Gynemed Media (GM501 Cult, GM501 Wash with phenol red and gentamicin, GM501 SpermStore and GM501 VitriStore) have been indeed analysed in the validation study. Therefore, it can be considered that suitability for the validated HPLC method had been acceptably shown.

Additionally, the method description of the Quantitative control test - Albumin concentration determination by HPLC-reversed phase has been included in detail in the updated Module 3.2.P (Final Control tests of the ancillary

human blood derivative in the medical device). It should be noted that it was noticed that in the provided results (overview of 3 recent batches for each product), the product specification of HSA concentration do not correspond to the release acceptance criteria set for the concentration of human serum albumin in Module 3.2.P, Specification (s) (this section has to be amended too with the correct specifications range for four (4) media), the applicant has not amended it to the correct specification range established in the correspondent section. This is considered an editorial mistake and it is not further pursued. It is highlighted as a recommended measure for the notification body (see section 7. Recommended measures to the notified body).

Furthermore, with regard to the reference standards, information about them has been included in the same section (3.4.3. Final Control tests of the ancillary human blood derivative in the medical device, together with the method description of Albumin concentration determination by HPLC-reversed phase), as requested. Particularly, it has been indicated that "with each HPLC run, 6 standards are included: i.e. aqueous solutions of 0.5, 1, 2.5, 5, 10, 15 mg/mL, prepared by dilution of the 25% HSA stock solution with ultrapure water. Ultrapure water is used as blank. Standards are always freshly prepared".

Release and shelf specifications are provided for each device, which include a specification range for the amount of albumin. Depending on the media, the amount of albumin is tested as either a test for "Total protein concentration (g/l)" (for VitriStore, GentleVit and PVP media) or as a test for "Concentration Human Serum Albumin", for the other media. As stated previously in the report, it will be recommended to the Notified Body to request the applicant to revise these release specifications of VitriStore Freeze Medium 2 and VitriStore Thaw Medium 1, 2 and 3 accordingly.

Batch analysis data has been provided in the dossier for all media. The results show compliance with the specifications set and consistency in the production. In addition to the above, a tabulated summary of the batch analyses manufactured between 2022 and 2023 of each media is provided. These batches are analysed for their human serum albumin concentration. All the results are within the specification limits established for each media. Additionally, it also specifies the batch of human serum albumin used for manufacturing each batch of Gynemed, thus ensuring traceability. At first, it was not indicated if the albumin comes from either Plasbumin 25% or Albunorm 25%. The applicant has provided quality data from batches manufactured with albumin sourced from either Octapharma or Grifols.

In addition, it was noticed that in the Certificates of Analysis provided, the test of determination of HSA content was missing as well as only three (3) CoAs of three (3) media were provided. Consequently, in the Applicant responses, representative Certificates of Analysis of recent batches of each media (manufactured between June and July, 2025) have been included. In these CoAs all quality parameters listed in 5.1. Specification (s) have been reported. In relation to the quality parameter "Concentration HSA" the specification range (maximum and minimum acceptance limits) is also indicated and match with the acceptance limits established in 5.1. Specification(s). In this respect, for all CoAs enclosed, all results for the parameter "Concentration HSA" are within the specifications established. However, for the "Concentration HSA" parameter in the CoAs of VitriStore Freeze Medium 2 and VitriStore Thaw Medium 1, 2 and 3, the release specifications now do not match the 80-120% approach of the declared content (see section 7. Recommended measures to the notified body).

Moreover, as also requested, the applicant has confirmed that albumin content is tested before release of each batch of each media.

Results were provided at release and at stability, all of which met acceptance criteria.

There appeared to be no differences in results of the quality attributes tested at release and during stability studies conducted on batches using albumin sourced from either Octapharma or from Grifols.

The albumin composition acceptance criteria is considered acceptable.

2.2.2.6. Stability

Summarized results of stability studies have been enclosed. A shelf life unopened of 6 months (for GM501 Wash media and GM501 Cult media), 9 months (for GM501 PVP), 12 months (for GM501 VitriStore Freeze/Thaw, GM501 GentleVit Freeze/Thaw and GM501 Hyaluronidase) and 18 months (for GM501 SpermStore) in the proposed storage conditions of 2–8°C, protected from sunlight; and the proposed in use shelf-life of all media for at least 7 days after bottle opening, are supported by respective stability data for Gynemed. In addition, a transport stress testing shows it also remains stable following 5 days exposure to 37°C (transport stress test). The proposed shelf-lives are considered acceptable.

The content of albumin is included in the stability studies conducted on the devices as measured by HPLC. In addition, pH, osmolality (if applicable), viscosity (if applicable), endotoxin concentration, gentamicin concentration (if applicable) are measured. Specifically for these devices the stability protocol also included the Mouse Embryo Assay (MEA) and Human Sperm Survival Assay (HSSA*).* The stability acceptance criteria for albumin concentration are unchanged from the release criteria. The albumin concentration remained with in specification and there was no degradation noted during the mentioned real-time testing (using product past its expiry date), transport stress testing (involving incubation of expired product at 37°C for 5 days) and in-use testing (opening container each workday during one week for 15 minutes using aseptic techniques).

This confirmed that the albumin (as Plasbumin 25% or Albunorm 25%) remained stable in each medium over the course of the shelf-life, when in use for 7 days and for up to 5 days exposure to 37°C.

In relation to the container closure system for Gynemed, full details have been provided on the immediate packing of the medical devices which are stated as packaged in type 1, glass containers with Ph. Eur. compliant Flurotec-coated stoppers (detailed drawings are provided). Based on the stability results provided, the container choice would appear to be appropriate for maintaining the quality of the device and the albumin content during its shelf-life.

Labelling and Information for Use (IFU)

There were some inconsistencies noted with in the Information for Use and the labelling with respect to the declaration of the albumin content, which is stated in Module 3, Table 1, as shown above.

Information for User

After clarification, the applicant confirmed that all of the IFU albumin content values are correct and the information is now aligned and updated.

With regard to Labelling:

Updated labelling, which are deemed to be correct, have been provided for the following labels:

- GM501 VitriStore Thaw Medium 3 (stated as containing 20 g/l albumin)
- GM501 GentleVit Freeze Medium 5 (stated as containing 11 g/l albumin)
- GM501 GentleVit Thaw Medium 3 (stated as containing 19 g/l albumin)
- GM501 GentleVit Thaw Medium 5 (stated as containing 20 g/l albumin)
- GM501 GentleVit Freeze Kit (outer label stated as containing 11-20g albumin)

The albumin declarations provided in the updated labels correspond to the information provided in Table 1 and it appears the labelling follows the convention of rounding to no decimal place. All other outstanding labelling queries are resolved and there are no outstanding labelling queries.

2.2.3. Discussion and conclusion on chemical, pharmaceutical and biological aspects

All Gynemed media contain HSA as an ancillary substance. Gynemed uses Plasbumin 25% (Grifols) or Albunorm 25% (Octapharma) which are both 25% Ph. Eur. Human Albumin Solutions and are manufactured under GMP requirements. The MOs raised requesting clarifications of the responsibilities and GMP inspection status of the manufacturing and testing sites have been satisfactory resolved.

A MO was raised on the risk of B19 Human parvovirus transmission when incorporating HSA into ART media systems. The Applicant have clarified this point and the MO was considered solved.

The major objection relating to the missing information on nitrosamines risk evaluation has been acceptably resolved.

For Plasbumin 25% a summarized dossier and an excipient file has been provided, whereas for Albunorm 25% a complete dossier has been provided. It is considered sufficient for this assessment as both adequately describes the composition, manufacture, shelf-life specification, stability data and viral safety. The applicant has declared that the used plasma complies with the current version of the approved Plasma Master File (PMF) certificates and has submitted the current version of both certificates - PMF certificates EMEA/H/PMF/000002/04/II/041/G (Grifols) and EMEA/H/PMF/000008/05/II/034/G (Octapharma) for Plasbumin 25% and Albunorm 25% respectively.

In summary, the information provided is considered adequate and the albumin used in the Gynemed medical device has been demonstrated to be of sufficient quality for its intended purpose.

Information provided is considered adequate:

- For the HSA as ancillary substance of the medical device, Gynemed, a complete "Drug Product" section has been provided together with several annexes where is located all the information of the medical device is provided.

The manufacturing process of Gynemed has been properly described and validated, a flowchart is provided. The remaining sections are also addressed properly, leading to the conclusion that the controls on the HSA, as well as on the rest of the constituents are appropriate. A validated HPLC method is used for the quantify the content of HSA in each medium, and the issues which remained unsolved have been satisfactorily resolved.

The content of Albumin in some devices has been clarified as well as the inconsistencies that were between the labels and IFU and the information provided in Module 3. Lastly, results of the stability studies carried

out for all media support the stability of Plasbumin 25% and Albunorm 25% throughout the shelf life of the Gynemed media.

2.3. Non-clinical documentation

2.3.1.1. Pharmacodynamics

The role of albumin in cell culture media has been adequately reviewed by the Applicant. HSA is currently universally added to most ART media because it is widely considered to be of benefit. The list of putative roles of albumin in culture media is extensive and includes:

- pH regulator
- Osmotic regulator
- Stabilization of cell membrane
- Nutrient and carrier of growth promoting substances (i.e., amino acids, vitamins, fatty acids, hormones, growth factors)
- Aid in fertilization process (important in the process of sperm capacitation and/or the acrosome reaction)
- Scavenger (of for example toxins and waste products from cell metabolism)
- Surfactant (anti-adhesion), thereby facilitating gamete and embryo manipulation -Cryoprotectant (increase viscosity of cryoprotectant solution).

2.3.1.2. Pharmacokinetics

Gynemed GmbH & Co. KG's HSA-containing ART media pose no pharmacokinetic concerns as they are not intended for intravenous use and have negligible contact with mucosal membranes.

2.3.1.3. Toxicity

General information from the *EMA Guideline on core SmPC for human albumin solution (CHMP/BPWP/494462/2011/Rev.3)* highlights key aspects related to the toxicity profile of human albumin. Human albumin, a natural component of human plasma, functions similarly to physiological albumin. Single-dose toxicity testing in animals is considered of limited relevance and does not facilitate the evaluation of toxic or lethal doses or a dose-response relationship. Repeated-dose toxicity testing is also impractical due to antibody development against heterologous proteins in animal models. To date, there have been no reports linking human albumin to embryo-foetal toxicity, oncogenic or mutagenic potential, and no acute toxicity has been observed in animal studies.

The toxicity data show that Gynemed GmbH & Co. KG's HSA-containing ART media have been subjected to comprehensive safety assessments, including Mouse Embryo Assays and Sperm Survival Tests, with minimal indications of toxicity. These media have been available on the market for an extended period and have been tested following ISO 10993-5 standards for cytotoxicity. The conclusion from the applicant that further in vivo testing is unnecessary is supported by a record of safe use and considerations of animal welfare. This

evidence supports the sufficiency of current testing protocols in evaluating the safety of the media without performing additional in vivo tests.

2.3.1.4. Local tolerance

Most media come only in direct contact with human gametes / embryos. Only the devices intended for embryo transfer or IUI, i.e., GM501 CULT media, GM501 Wash media, come into direct contact with mucosal membrane. As a result, both the irritancy as the sensitizing potential were evaluated according to ISO 10993-10 for these media. All media meet requirements of the ISO 10993-10 guidelines.

2.3.2. Discussion and conclusion on the non-clinical documentation

Human serum albumin (HSA) is the most abundant protein in human blood plasma. It is well-characterised, and it has been used for decades as a plasma substitute.

Gynemed HSA-containing ART media are a range of media products manufactured by Gynemed GmbH & Co. KG containing human serum albumin25%, . HSA is classified in the pharmacotherapeutic group: immune sera and immunoglobulins: plasma substitutes and plasma protein fractions, ATC code: B05AA01.

No risks to human safety have been identified for the proposed use of Gynemed GmbH & Co. KG's HSA-containing ART media. The pharmacodynamic role of HSA in culture media has been clearly outlined, highlighting its beneficial properties such as pH regulation, osmotic regulation, membrane stabilization, nutrient transport, support for the fertilization process, scavenging of toxins, and surfactant action. Pharmacokinetic concerns are negligible as the product is not administered intravenously. Toxicity data indicate that no significant toxic, mutagenic, or oncogenic risks are associated with HSA. Long-term use and compliance with ISO standards support the sufficiency of existing safety protocols without the need for further in vivo tests. Local tolerance assessments confirm compliance with ISO 10993-10. Overall, the documentation submitted confirms comprehensive safety evaluations and regulatory adherence.

According to the *Guideline on the environmental risk assessment of medicinal products for human use* (*EMEA/CHMP/SWP/4447/00 rev1, 2024*), based on the nature of the substance, no environmental risk is expected. As such, the applicant justifies the absence of ERA studies.

2.4. Clinical evaluation

2.4.1. Usefulness of the ancillary medicinal substance incorporated in the medical device as verified by notified body

Function of Human Albumin Solution (HAS) in assisted reproductive techniques (ART) products

Albumin is the most abundant macromolecule that gametes come into contact within the human oviduct; it can be incorporated by the embryo, it binds lipids and may help to bind and stabilize growth factors. This positive contribution to embryo development in vivo also holds true for its usage in in vitro fertilization techniques. By binding growth-promoting substances and controlling their release at cellular level, albumin may add potential to the medium. Indeed, albumin has been shown to support the embryo physiology and

metabolism. The use of HSA in embryo culture media has also been recommended by the European Society of Human Reproduction and Embryology (ESHRE).

Gynemed GmbH & Co. KG HSA-containing ART media are a range of media products designed for the use in ART. They are used in specialized laboratories performing fertilization techniques, including In Vitro Fertilization (IVF), Intra Cytoplasmatic Sperm Injection (ICSI) and sperm preparation / analysis. The intended users are IVF professionals (lab technicians, embryologists, or medical doctors).

The media come in direct physical contact with human gametes or embryos and/or uterus mucosal membrane during intrauterine insemination/embryo transfer.

The following HSAs are used by Gynemed GmbH & Co. KG:

- Plasbumin 25% (alternative name: Albumin (human) 25%), manufactured by Grifols
- Albunorm (alternative name: Albumin (human) 25%), manufactured by Octapharma

Both human albumin solutions are manufactured from human plasma that is covered by an EMA-approved Plasma Master File and all batches of Plasbumin 25% or Albunorm used by Gynemed GmbH & Co. KG have an official EU and FDA medicinal release certificate.

The HSA included in ART media has an action ancillary to the media and is intended to optimize the media performances. The amount of Plasbumin 25% or Albunorm added to ART media is dependent on the type of medium and ranges from 3.2g/L to 24 g/L. There is no manipulation of the human albumin solutions before adding them to the ART media from the manufacturer.

The ancillary roles of HSA to the Gynemed GmbH & Co. KG HSA-containing ART media are multiple and include:

- pH regulation
- Osmotic regulation
- Stabilization of cell membrane
- Nutrient and carrier of growth promoting substance (i.e. amino acids, vitamins, fatty acids, hormones, growth factors)
- Aid in fertilization process (important in the process of sperm capacitation and /or the acrosome reaction)
- Scavenger (of for example toxins and waste products from cell metabolism)
- Surfactant (anti-adhesion, thereby facilitating gamete and embryo manipulation)
- Cryoprotectant (increase viscosity of cryoprotectant solution) (only applicable for following Gynemed GmbH & Co. KG HSA-containing ART media: GM501 SpermStore, GM501 VitriStore Freeze / Thaw, GM501 GentleVit Freeze / Thaw)

The intended use of Gynemed GmbH & Co. KG HSA-containing ART media depends on the type of medium and is described in Table 1 below:

Table 9. Intended purpose of the medical device

Device Name	Intended Purpose
GM 01 SpermStore	GM501 SpermStore is a cell culture medium for the cryopreservation of human spermatozoa.
GM501 PVP	GM501 PVP is a ready-to-use viscous medium that can be used in ICSI procedures. These procedures require the capture of individual sperm cells in a pipette for injection into the oocyte. This is facilitated by first immobilizing the sperm by placing them in a viscous medium prior to nicking the tail to immobilize the sperm completely.
GM501 Hyaluronidase	This medium is typically used in the oocyte denudation process for the digestion of the hyaluronic acid between cumulus cells.
GM501 VitriStore Freeze/Thaw Kit	The GM501 VitriStore Freeze / Thaw kit consists of a set of media for vitrification and warming of human embryos (morula till blastocyst stage).
GM501 GentleVit Freeze/Thaw Kit	The GM501 GentleVit Freeze / Thaw kit consists of a set of media for vitrification and warming of human oocytes and human embryos (zygote till blastocyst).
GM501 Washing Media Kit	GM501 Washing media are ready-to-use media designed for washing procedures of oocytes and embryos and any short-term handling procedures of these cells outside the incubator. GM501 Washing media can also be used for embryo transfer. GM501 SpermActive and GM501 SpermAir are ready-to-use media designed for all sperm preparation, sperm washing, IUI and swim up techniques like density-gradient centrifugation as well as for testicular tissue.
GM501 Cult Media Kit	GM501 Cult media are ready-to-use bicarbonate-buffered culture media, designed for fertilization and for all embryo culture from day 1 to blastocyst stage. They can also be used for embryo transfer.

The applicant mainly provided peer-reviewed manuscripts for the clinical evaluation outcome report to support the usefulness of the inclusion of the ancillary medicinal substance in the device. This is considered acceptable, based on the following reasons:

- Since the early 1990s, HSA is universally added to ART media because it is widely considered to be of benefit.
- Both human albumin solutions that are used by Gynemed GmbH & Co. KG are manufactured from human plasma that is covered by an EMA-approved Plasma Master File.

Both human albumin solutions are released on the market with an EU/FDA official medical release certificate.

2.4.2. Clinical safety of the ancillary medicinal substance incorporated in the medical device

One of the main safety issues arising from the use of culture media containing HSA is the possible risks that the mother and embryo may be exposed to during in vitro fertilization protocols. Indeed, bacterial contamination, transmitting viral/prion contaminations and local irritant effects from the culture media poses the greatest risks to the health of the patient.

Considering the manufacturing controls employed for the production of the human serum albumin and the overall reduction factors obtained from the adventitious safety validation studies, human serum albumin manufacturing process appears to be capable of reducing the prions/viral load of potential adventitious agents. Both (from Grifols and Octapharma) human albumin solutions that are used by Gynemed GmbH &

Co. KG are manufactured from human plasma that is covered by an EMA-approved Plasma Master File. Also, both human albumin solutions are released on the market with an EU/FDA official medical release certificate. Taking into account the total amount of human serum albumin used during the different phases of an IVF treatment, the risk to gamete and mother can be considered very low/negligible. Therefore, it is considered that there is a low risk to patients undergoing IVF procedures.

As human albumin solution is considered as a critical component of the ART media, the manufacturer performs an additional incoming inspection before a batch of human albumin solution can be used in production.

Besides a check of the market authorisation certificates, the manufacturer performs the following internal quality control tests:

- Endotoxin concentration of the human albumin batch should be < 0.5 EU/ml.
- Albumin concentration of the human albumin batch should be in the range of 237.5-262.5g/L
- Mouse embryo assay (MEA) on standard culture medium supplemented with Plasbumin 25% or Albunorm to an end concentration of 1% HSA. Testing should be performed in two independent and accredited labs (Embryotech and EmbryoTools). Expanded blastocyst rate in both labs should be ≥ 80% blastocysts after 96 hours in culture. If the rate of expanded blastocysts is lower than 80% in both labs, such human albumin solution should preferably not be used for culture media containing ≥ 1% HSA in order to prevent the manufacturing of bathes that cannot be released due to failed MEA test as part of the quality control before release. Also, if the rate of expanded blastocysts is lower than 80% in both labs, the human albumin solution is subjected to a second MEA, in which standard culture medium is supplemented with 0.5% HSA. If this second test succeeds, the batch of human albumin solution can be released only for production of media with a concentration equal/below to 0.5% HSA.

The applicant also described below some that may raise safety issues associated with the use of HSA.

Safety concerns about the PRESENCE OF OCTANOIC ACID in human albumin solution:

Octanoic acid (also known as octanoate or sodium caprylate) is a stabilizer that is added during the manufacturing of HSA in order to protect the protein during the heat-inactivation of viruses. Biologically, octanoic acid disrupts the cells energy metabolism, reduces the intracellular pH, induces oxidative stress and is known to be cytotoxic at higher concentrations.

The applicant described a set of actions that allow mitigating the harmful effects of Octanoic acid:

- Gynemed GmbH & Co. KG performs an incoming inspection on each batch of HSA before it may be used for production of ART media: testing is performed by two independent and accredited labs at a concentration of 1%.
- Gynemed GmbH & Co. KG performs a strict quality control (including MEA- or HSSA3-testing) before a batch of ART media is released on the market. Importantly, quality control is performed on the finished product, and the used MEA- or HSSA protocol is according to the use of the product.
- Octapharma and Grifols have both determined release criteria for the concentration of octanoic acid in their HAS (0.064-0.096 mmol/g protein and 0.07 and 0.09 mmol/g respectively).
- These concentrations correspond with the accepted concentrations according to the FDA regulations (0.08 ± 0.016 mmol/g protein).

Concerns about the PRESENCE OF PHTHALATES in human albumin solution:

In a publication of Hughes et al. (2020) the effect of phthalates in HSA was highlighted. Phthalates are known endocrine disruptors which have negative effects on reproduction and ART procedures.

Generally, blood is stored in bags that contain di–2–ethylhexyl phthalate (DEHP). DEHP however is not covalently bound to the plastic which could cause leakage of DEHP into the stored blood. HSA is obtained by a fractionation process from human blood. Therefore, there is a potential that phthalate compounds first contaminate the stored blood and afterwards cofractionate with HSA. In addition, the presence of lipases in blood can lead to the conversion of DEHP to mono-ethylhexyl phthalate (MEHP) that accumulates in higher concentrations and is more toxic than the parent compound.

The applicant described a set of actions that allow mitigating the harmful effects of Phthalates

- Gynemed GmbH & Co. KG performs an incoming inspection on each batch of HAS before it may be used for production of ART media: testing is performed by two independent and accredited labs at a concentration of 1%.
- Gynemed GmbH & Co. KG performs a strict quality control (including MEA- or HSSA-testing) before a batch of ART media is released on the market. Importantly, quality control is performed on the finished product, and the used MEA- or HSSA protocol is according to the use of the product.

Considering the controls implemented by the manufacturers, the concerns outlined above are deemed to be mitigated and therefore do not constitute safety issues.

2.4.3. Clinical benefit/risk profile of the ancillary medicinal substance incorporated in the medical device

The applicant based on data obtained from the clinical use of HSA containing ART media in IVF centres or from peer reviewed literature, demonstrated the benefit of supplementing the culture media used in IVF protocols with HSA.

Human serum albumin in ART media has a well-established safety profile and the risks of adverse effects, listed above, are low as a result of the concentration used and the method of administration resulting in limited contact with the human body. The risk of viral transmission is controlled as part of the HSA manufacture as well as testing. The use of HSA in ART media is well established, has a positive benefit/ risk profile and the usefulness is confirmed.

2.4.4. Discussion and conclusion on the clinical evaluation

The applicant has submitted an application for the ancillary medicinal substance, HSA (Human Serum Albumin, 25%), to be used in a range of media (considered class III medical devices) for Assisted Reproduction Technology (ART)/ in vitro fertilisation (IVF). HSA-containing ART media are liquids used for storage, transportation and preservation of human gametes or embryos in vitro. HSA is universally added to most ART media because it is widely considered to be of benefit. The role of albumin in culture media is extensive, including pH regulation, osmotic regulation, stabilisation of cell membrane, nutrient and carrier of growth promoting substances (i.e. amino acids, vitamins, fatty acids, hormones, growth factors), aid in fertilisation process (important in the process of sperm capacitation and/or the acrosome reaction), scavenger (of for example toxins and waste products from cell metabolism), surfactant (anti-adhesion,

thereby facilitating gamete and embryo manipulation and cryoprotectant (increase viscosity of cryoprotectant solution). The applicant intends to use two sources of HSA, Plasbumin 25% (Grifols) and Albunorm (Octapharma), both of which have previously been granted a positive opinion by CHMP as part of other ancillary substance consultations.

Proteins, including HSA, are thought to stabilize the oocyte and embryonic cell membranes in an in vitro environment. This may be evident by improved fertilization and embryo quality after preincubation of oocytes before ICSI or IVF. Furthermore, in vitro culture and recovery of frozen-thawed blastocysts for up to 20 h before transfer increased three-fold the rate of blastocyst implantation. Proteins, specifically HSA, may serve as an essential and direct nutrient/nitrogen source for blastocyst stage embryos. This function may not be replaced by other macromolecular supplements.

Most embryo culture media are still supplemented with proteins rather than with nonprotein macromolecules or recombinant protein products. HSA is probably the most common supplement followed by globulin enriched preparations.

The applicant provided discussions on albumin's physiological roles, and, in addition, the medical device manufacturer submitted data obtained from the clinical use of HSA containing ART media in IVF centres or from peer reviewed literature, to demonstrate the usefulness of albumin supplementation of ART media. The Notified Body has verified the usefulness of HSA as part of the medical device media. In addition, the manufacturer has provided a clinical evaluation document, which discusses varying aspects of the ancillary medicinal substance added to the media, including a discussion on potential alternatives (globulins, hyaluronan and protein-free media). While the applicant did not submit any new clinical data, it is envisaged that, where well-known medicinal substances for established purposes are the subject of the consultation, all aspects of usefulness could be addressed by experience and other information widely available. As HSA is a well-known substance contained in several medicinal products as well as in comparable medical devices, the Notified Body´s conclusion that inclusion of the ancillary human blood derivative, HSA, in the IVF media is acceptable in terms of usefulness, is endorsed.

With respect to safety, HSA is a human blood derivative and as such, the main clinical risk of HSA is the transmission of viral or prion-carried diseases to a patient during embryo transfer and intra-uterine insemination during ART procedures. A number of risk reduction measures are employed by the applicant most of which are manufacturing based and referred to in the quality section of this report. Specific clinical risk reduction measures include warnings on the labels and instructions for use (IFU) that all blood products should be treated as potentially infectious. The Notified Body has outlined the well-established safety profile of human albumin and has clearly detailed the risks of human albumin used within these media, particularly the risk of transmissible infections, which are considered to be low.

The benefits and usefulness of HSA in ART media are well established and there are a number of comparable HSA supplemented ART media products available, which have received a positive CHMP consultation procedure opinion. Human albumin solutions incorporated in the media have an excellent viral safety record over years of clinical use. However, despite the rigorous quality controls, there is no known test method that can offer full assurance that products derived from human blood will not transmit infectious agents. The cell culture media should therefore still be treated as potentially infectious. However, the risk of transmission is considered to be low, and these risks are reduced to an acceptable level, by taking appropriate risk control measures. In conclusion, the safety profile for HSA used in the Gynemed GmbH & Co. KG HSA-containing ART media is considered to be well-established and no further issues are identified.

Overall, the benefit-risk balance for this product from a clinical standpoint is positive.

2.5. Overall conclusions

The quality documentation for the ancillary substances Plasbumin 25% and Albunorm 25% themselves and for the ancillary medicinal substances as incorporated in the medical device is considered adequate overall. The MO regarding the safety margin for the transmission to embryos of B19 Human parvovirus raised during the procedure has been satisfactorily resolved in the responses to the Day 180 LoQ. The remaining MOs and OCs raised on the nitrosamine risk evaluation and clarifications and GMP inspection status of several of the manufacturing and testing sites of Plasbumin 25% and Albunorm 25% were also satisfactorily resolved.

Additionally, clarifications requested related to HPLC method suitability, discrepancies about the Albumin content, clarifications on labelling and instructions for users were satisfactorily resolved, although there are still some editorial mistakes in the dossier that remained unsolved. These are highlighted as recommendations to the notified body, see section 7. *Recommended measures to the notified body.*

The pharmacological and pharmacokinetic profiles of HSA in ART media have been comprehensively reviewed, demonstrating its safety and extensive functional benefits. From a pharmacodynamic perspective, HSA plays a critical role in ART media, contributing to pH and osmotic regulation, stabilization of cell membranes, nutrient transport, and detoxification. It is integral to sperm capacitation, acrosome reaction, and embryo handling, enhancing embryonic quality and pregnancy outcomes. Additionally, HSA acts as a cryoprotectant and prevents cellular adhesion, further facilitating gamete and embryo manipulation. Historical and recent studies consistently highlight HSA's superiority as a chemically defined protein supplement in ART media. From a pharmacokinetic perspective, the negligible exposure of patients to HSA-containing media during procedures like embryo transfer and intra-uterine injection ensures safety. The minimal volume of HSA used, combined with its well-understood degradation and metabolic pathways, alleviates any concerns regarding systemic effects.

Based on the nature of the substance (albumin), no environmental risk is expected according to the Guideline EMEA/CHMP/SWP/4447/00 rev1, 2024.

Given the demonstrated benefits of HSA, the usefulness of its addition to ART media and the low safety risk associated with its use in assisted reproduction techniques, the benefit-risk of ART media supplemented with HSA (Gynemed) is considered positive from a clinical perspective,

In conclusion, the information provided on Gynemed GmbH & Co. KG HSA-containing ART media is considered acceptable and the application is recommended for a positive opinion.

2.6. Recommendation

Based on the CHMP review of data submitted, the CHMP considered by consensus that the quality and safety including the benefit risk profile of Human serum albumin used as ancillary medicinal substance(s) in the Gynemed GmbH & Co. KG HSA-containing ART media was favourable and therefore granted a positive opinion in the consultation procedure.